Exhibit 3

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SANTA BARBARA • SANTA CRUZ

SCHOOL OF PHARMACY
DEPARTMENT OF PHARMACEUTICAL CHEMISTRY

SAN FRANCISCO, CALIFORNIA 94143

February 11, 1982

Hadrian R. Katz
Arnold & Porter
1200 New Hampshire Avenue, N.W.
Washington D.C. 20036

Dear Mr. Katz:

I have studied the documents you sent to me concerning the continine studies performed by Dr. G.B. Gori and the pharmacokinetic model studies by Drs. T.D. Darby and J.E. McNamee. I also have discussed these studies with colleagues who are familiar with research in these areas. In the comments that follow, I will attempt to summarize the overall scientific merit of these two studies. Although there are aspects of these studies which have merit, on balance, I am not convinced that based on these studies one can conclude that Barclay's tar delivery is equal to that of other cigarettes with FTC testing measurements of one milligram.

It is well established that the tobacco alkaloid nicotine is rapidly metabolized in mammals including man. A variety of metabolites have been characterized both in vitro and in vivo. The most prominent metabolic pathway for nicotine in mammals is its conversion to the lacatam cotinine. This process occurs in two stages and involves the production of an intermediate carbinolamine followed by a second oxidation to cotinine itself. Cotinine is further metabolized to cotinine-N-oxide and trans-3'-hydroxycotinine. Analytical procedures for cotinine that require thermolysis (e.g. GLC) should take into account the possibility that a given biological sample may contain varying quantities of cotinine-N-oxide which may undergo thermal reduction to cotinine and thus lead to a false estimate of cotinine levels.

The nitrogen-phosphorous GLC detector used by Gori should provide adequate sensitivity for the estimation of human plasma cotinine levels. However, it is difficult to assess the accuracy of the data generated in these studies because of the scarcity of methodological details. Furthermore, since Dr. Gori did not employ an internal standard in his assay, the recovery data are likely to be very unreliable. Cotinine is extracted from plasma into organic solvents only with difficulty and emulsions often cause significant changes in extraction efficiency. Furthermore, water definitely is not a proper vehicle with which to perform recovery experiments. Consequently, plasma cotinine levels determined without the aid of an internal standard and based on poorly designed recovery data would at best provide only a crude estimate of the true values.

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I agree with Dr. Gori that, in theory, cotinine levels can provide a reasonable estimate of nicotine exposure. There are, however, a number of problems associated with the quantitative estimation of cotinine in plasma which have not been fully addressed by the Gori study. Confidence in the results will be particularly dependent upon an established dose versus plasma level correlation. Dr. Gori raises this issue himself on page 4 of his report when he states that "the relationship of smoke residues in smokers of high yield cigarettes does not follow a 1:1 proportion, when matched to the nominal FTC yield of the cigarette smoked." In the absence of such an experimentally determined correlation, the accuracy of the estimated nicotine exposures, when based on cotinine blood levels, will be questionable.

Finally, I am somewhat disturbed by the tacit assumption that nicotine and tar levels as determined by a standard machine test can be correlated with cotinine blood levels. In my opinion extensive "dose-response" studies would have to be conducted to justify any conclusions which assume such a relationship.

The pharmacokinetic model proposed by Darby and McNamee is reasonable to the extent that the long half-life of cotinine and short half-life of nicotine allow, in theory, one to calculate approximate nicotine exposure levels based on cotinine plasma levels. However, the practical value of the model will clearly depend on the accuracy of the parameters used in its design and application. The model should be tested with a wider range of experimental data in order to properly assess its utility and to establish the validity of the various assumptions used in its development. Although I must admit to a bias, in my opinion pharmacokinetic models of this type that are not thoroughly tested with experimentally derived data are of limited value.

Sincerely yours,

Neal Castagnoli

Neal Castagnoli, Ph.D.
Professor of Chemistry and
Pharmaceutical Chemistry

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